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Ancillary Therapy and Supportive Care of Chronic Graft-versus-Host Disease: National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: V. Ancillary Therapy and Supportive Care Working Group Report

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ABSTRACT

The Ancillary Therapy and Supportive Care Working Group had 3 goals: (1) to establish guidelines for ancillary therapy and supportive care in chronic graft-versus-host disease (GVHD), including treatment for symptoms and recommendations for patient education, preventive measures, and appropriate follow-up; (2) to provide guidelines for the prevention and management of infections and other common complications of treatment for chronic GVHD; and (3) to highlight the areas with the greatest need for clinical research. The definition of "ancillary therapy and supportive care" embraces the most frequent immunosuppressive or anti-inflammatory interventions used with topical intent and any other interventions directed at organ-specific control of symptoms or complications resulting from GVHD and its therapy. Also included in the definition are educational, preventive, and psychosocial interventions with this same objective. Recommendations are organized according to the strength and quality of evidence supporting them and cover the most commonly involved organs, including the skin, mouth, female genital tract, eyes, gastrointestinal tract, and lungs. Recommendations are provided for prevention of infections, osteoporosis, and steroid myopathy and management of neurocognitive and psychosocial adverse effects related to chronic GVHD. Optimal care of patients with chronic GVHD often requires a multidisciplinary approach.

The opinions expressed here are those of the authors and do not represent the official position of the National Institutes of Health, Food and Drug Administration, or the United States Government.

KEY WORDS
Chronic graft-versus-host disease • Allogeneic cell transplantation • Supportive care • Consensus

INTRODUCTION

Chronic graft-versus-host disease (GVHD) is characterized by polymorphic clinical manifestations with varying severity and clinical course. Prolonged systemic immunosuppressive treatment including corticosteroids is necessary to control disease severity and decrease nonrelapse mortality. Treatment, combined with the delayed immunologic reconstitution associated with chronic GVHD, increases the risk of infections and other complications. Clinical manifestations of chronic GVHD can persist for prolonged periods, causing significant morbidity, and some may be irreversible. Thus, ancillary therapy and supportive care become central components in the long-term management of chronic GVHD after allogeneic hematopoietic cell transplantation (HCT).

PURPOSE OF THIS DOCUMENT

The Ancillary Therapy and Supportive Care Working Group had 3 goals: (1) to establish guidelines for ancillary therapy and supportive care in chronic GVHD, including treatment for symptoms and recommendations for patient education, preventive measures, and appropriate follow-up; (2) to provide guidelines for the prevention and management of infections and other common complications; and (3) to highlight the areas in supportive care with the greatest need for clinical research.

In this document, the term "ancillary therapy and supportive care" embraces the most frequent immunosuppressive or anti-inflammatory interventions with topical intent and any other intervention directed at organ-specific control of symptoms or complications resulting from GVHD and its therapy. Also included in this definition are educational, preventive, and psychosocial interventions with this same objective. Several important aspects of diagnosis and good follow-up care, such as monitoring for and management of medication toxicities (hypertension, hyperlipidemia, renal dysfunction, seizures, etc) and problems not directly related to chronic GVHD (eg, iron overload, psychosocial adaptation) could not be included in this review. Interested readers are referred to other publications [1-3].

The committee's recommendations are organized according to an evidence-based system to reflect the strength of recommendations and the quality of evidence supporting them (Appendix). It is hoped that these recommendations will serve as a platform for recognizing areas in need of cooperative clinical research projects. A version of this document posted on the Internet (www.asbmt.org/GvHDForms) includes additional specific dispensary information.

The Working Group wishes to emphasize that the recommendations in this document represent a wide variety of generally accepted current medical practices. Good clinical judgment and individual circumstances should determine appropriate interventions for specific patients.

SUMMARY OF RECOMMENDATIONS

Table 1 provides a summary of ancillary therapy and supportive care interventions that is categorized by organ system. Table 2 provides a summary of general monitoring recommended for patients who are diagnosed with chronic GVHD.

SKIN AND APPENDAGES

See Table 3. Ancillary and supportive care of the skin and appendages focuses on prevention, management of manifestations such as pruritus, rash, pain, dyspigmentation, and limited range of motion and topical care for erosions, ulcerations, and superinfection. Topical therapy plays an important role in alleviating symptoms and treating complications caused by loss of skin integrity and immunosuppression. In the absence of poor prognostic factors such as thrombocytopenia ($<100\ 000/\mu L$), treatment with corticosteroids at the time of diagnosis of chronic GVHD, cutaneous involvement of $>50\%$ of total body surface, and a moderate or severe overall global score, topical agents can serve as the primary treatment for cutaneous chronic GVHD. Because skin cancer incidence is increased in patients with chronic GVHD, biopsy should be obtained whenever clinically indicated.

Measures to Prevent the Development or Exacerbation of GVHD

UV radiation can cause exacerbation of cutaneous GVHD [4]. Photoprotection includes protective clothing, sun avoidance, physical sunblocks, and sunscreens. Topically applied agents should protect against UV-A and UV-B. Micronized zinc, micronized titanium dioxide, Mexoryl SX, or Parsol 1789 (avobenzone) are useful additives to ensure adequate UV-A protection. Rinse-cycle additives can enhance the barrier function of clothing.

Topical Care and Therapies: Intact Skin

Regular lubrication of dry but intact skin with emollients may decrease pruritus and maintain skin

Table 1. *Summary of Ancillary Therapy and Supportive Care Interventions*

Organ System	Organ-Specific Intervention*
Skin and appendages	**Prevention** **Photoprotection. Surveillance for malignancy.** **Treatment** **For intact skin — Topical emollients, corticosteroids, antipruritic agents, and others (eg, psoralen–UV-A, calcineurin inhibitors).** **For erosions/ulcerations — Microbiologic cultures, topical antimicrobials, protective films or other dressings, debridement, hyperbaric oxygen, wound care specialist consultation.**
Mouth and oral cavity	**Prevention** **Maintain good oral/dental hygiene. Consider routine dental cleaning and endocarditis prophylaxis. Surveillance for infection and malignancy.** **Treatment** **Topical high and ultra-high potency corticosteroids and analgesics. Therapy for oral dryness.**
Eyes	**Prevention** **Photoprotection. Surveillance for infection, cataract formation, and increased intraocular pressure.** **Treatment** **Artificial tears, ocular ointments, topical corticosteroids or cyclosporine, punctal occlusion, humidified environment, occlusive eye wear, moisture chamber eyeglasses, cevimeline, pilocarpine, tarsorraphy, gas-permeable scleral contact lens, autologous serum, microbiologic cultures, topical antimicrobials, doxycycline.**
Vulva and vagina	**Prevention** **Surveillance for estrogen deficiency, infection (herpes simplex virus, human papilloma virus, yeast, bacteria), malignancy.** **Treatment** **Water-based lubricants, topical estrogens, topical corticosteroids or calcineurin inhibitors, dilators, surgery for extensive synechiae/obliteration, early gynecologic consultation.**
Gastrointestinal tract and liver	**Prevention** **Surveillance for infection (viral, fungal).** **Treatment** **Eliminate other potential etiologies. Dietary modification, enzyme supplementation for malabsorption, gastroesophageal reflux management, esophageal dilatation, ursodeoxycholic acid.**
Lungs	**Prevention** **Surveillance for infection (*Pneumocystis carinii,* viral, fungal, bacterial).** **Treatment** **Eliminate other potential etiologies (eg, infection, gastroesophageal reflux). Inhaled corticosteroids, bronchodilators, supplementary oxygen, pulmonary rehabilitation. Consideration of lung transplantation in appropriate candidates.**
Hematopoietic	**Prevention** **Surveillance for infection (cytomegalovirus, parvovirus).** **Treatment** **Eliminate other potential etiologies (eg, drug toxicity, infection). Hematopoietic growth factors, immunoglobulin for immune cytopenias.**
Neurologic	**Prevention** **Calcineurin drug-level monitoring. Seizure prophylaxis including blood pressure control, electrolyte replacement, anticonvulsants.** **Treatment** **Occupational and physical therapies, treatment of neuropathic syndromes with tricyclic antidepressants, selective serotonin reuptake inhibitors, or anticonvulsants.**
Immunologic and infectious diseases	**Prevention** **Immunizations and prophylaxis against *Pneumocystis carinii,* varicella zoster virus, and encapsulated bacteria based on guideline of the Centers for Disease Control. Consider immunoglobulin replacement based on levels and recurrent infections. No current evidence supports the use of mold-active agents. Surveillance for infection (viral, bacterial, fungal, atypical).** **Treatment** **Organism-specific antimicrobial agents. Empiric parenteral broad-spectrum antibacterial coverage for fever.**
Musculoskeletal	**Prevention** **Surveillance for decreased range of motion, bone densitometry, calcium levels and 25-OH vitamin D. Physical therapy, calcium, vitamin D, bisphosphonates.** **Treatment** **Physical therapy, bisphosphonates for osteopenia and osteoporosis.**

*In general, close serial monitoring of all organ systems is recommended to promote early detection and intervention directed toward reversing or preventing progression of chronic GVHD manifestations and treatment-associated toxicities. Ancillary and supportive care therapies are commonly employed *in addition to* systemic GVHD treatment, although in some cases their use may circumvent the need for systemic treatment or allow doses of systemic agents to be decreased.

Table 2. *Summary of Monitoring Recommendations**

Interval history with symptom assessment (including psychosocial symptoms) and medication review (every 1-12 mo)
Physical examination (every 1-12 mo)
Weight (every 1-6 mo)
Height (adults: every 12 mo; children and adolescents: every 3-12 mo)
Nutritional assessment (every 1-12 mo)
Tanner score (children and adolescents: every 6-12 mo)
Developmental assessment (children and adolescents: every 3-12 mo)
Laboratory monitoring
Complete blood cell counts with differential (every 1-6 mo)
Chemistry panel including renal and liver function tests (every 1-6 mo)
Therapeutic drug monitoring (every 1-6 mo)
IgG level (every 1-6 mo until normal independent of replacement)
Lipid profile (every 6-12 mo during treatment with corticosteroids or sirolimus)
Iron indices (every 6-12 mo if red blood cell transfusions are required or if iron overload has been documented previously)
Pulmonary function tests (every 3-12 mo)
Endocrine function evaluation, eg, thyroid function tests, bone densitometry, calcium levels, 25-OH vitamin D (every 12 mo)
Subspecialty evaluations
Ophthalmology with Schirmer test and glaucoma assessment (every 3-12 mo)
Dental or oral medicine with comprehensive soft and hard tissue examination, culture, biopsy or photographs of lesions (as clinically indicated), and radiographs (every 6-12 mo)
Dermatology with assessment of extent and type of skin involvement, biopsy, or photographs (as clinically indicated)
Gynecology for vulvar or vaginal involvement (as clinically indicated)
Physiotherapy with assessment of range of motion (every 3-12 mo if sclerotic features are present)
Neuropsychological testing (every 12 mo as clinically indicated)

*All organ systems potentially affected by chronic GVHD or its treatment [3] should be monitored serially in individuals at risk at least annually for 5 years after HCT. The scope and frequency of monitoring should be individualized as clinically indicated. More frequent monitoring is strongly advised for those with active GVHD, especially during high-risk periods (eg, treatment taper or escalation), and for those who are participating in clinical trials.

Table 3. *Ancillary Therapy and Supportive Care Recommendations for Skin and Appendage GVHD**

Type of Intervention	Recommendation Rating
Preventive measures	
Photoprotection: UV-A and UV-B blockade including	
Avoidance of sun exposure (especially between 10:00 AM and 4:00 PM)	AIII
Use of sunscreens (SPF ≥20 with broad-spectrum UV-A and UV-B protection)	AIII
Protective clothing	AIII
Treatment	
Intact Skin	
Symptomatic treatment with emollients and anti-pruritic agents	AIII
Topical corticosteroids	CIIb
Light therapy (PUVA, UV-A1, UV-B, narrow band UV-B)	CIIa
Topical calcineurin inhibitors (pimecrolimus, tacrolimus)	CIIa
Sclerotic manifestations with joint stiffness or contractures	
Deep muscle/fascial massage (Heller works) to improve ROM	CIII
Stretching exercises to improve ROM	BIII
Erosions and ulcerations	
Topical or oral antimicrobials	BIII
Wound dressings and debridement	CIII
Control of edema	BIII
Pediatric considerations	
Systemic side effects of topical steroids may occur more frequently in children because of the larger skin surface area-to-body weight ratio	
Although the least potent topical steroids (1-2.5% hydrocortisone) are safe, middle to upper mid-strength topical steroids should generally be used sparingly, and on limited areas, for ≤3-4 wk	
Topical steroids under occlusive dressings are not recommended	
The use of potent or superpotent steroids on the face or at any site in infants <1 y of age is not recommended	

*SPF indicates sun protection factor; PUVA, psoralen–UV-A; ROM, range of motion.

integrity. Ointments and creams are better emollients than are lotions, and these agents are less likely to sting when applied to erythematous skin.

Nonsclerotic skin lesions without erosions or ulcerations (lichen planus-like or papulosquamous plaques) may respond well to topical steroids and emollients. Long-term use of topical steroids may be complicated by local skin atrophy and development of striae.

1. General guidelines regarding topical steroid recommendations for skin GVHD.
   a. From the neck down: Treatment should begin with mid-strength topical steroids (eg, triamcinolone .1% cream or ointment). In unresponsive cases, short-term occlusion of mid-strength steroids with damp towels ("wet wraps") increases skin hydration and steroid penetration. When this is impractical, higher potency steroids (eg, fluocinonide .05% cream or ointment) may be helpful. The most potent topical steroids (eg, clobetasol dipropionate .05%, halobetasol propionate .05%) should not be used under occlusion. The use of wet wraps and high potency steroids should be limited to <14 consecutive days, if possible.
   b. Face, axillae and groin: Lower potency steroids (hydrocortisone 1-2.5%, desonide .05%) are preferable for long-term use.
   c. Emollients: These may be used after the application of steroids. Emollients are occlusive and may increase the potency of steroids.

2. Antipruritics: Although pruritus related to GVHD generally responds to immunosuppressive therapy, other adjuvant treatments may be useful.
   a. Topical: Hydrocortisone/pramoxine or menthol-based creams/lotions.
   b. Systemic: Antihistamines (eg, diphenhydramine, hydroxyzine, ranitidine) or the tricyclic agent doxepin can be given.
3. Others interventions.
   a. Psoralen with UV-A [5-7], UV-A1 (340-400 nm) [8], UV-B [9], or narrowband UV-B (311-313 nm) [10] can be effective, especially if sclerosis is not present. Phototherapy may be administered 2-3 times per week by dermatologists.

      Cautionary note: Phototherapy is associated with an increased risk of skin cancer. A history of skin cancer, aphakia, or photosensitivity may be a contraindication to phototherapy.
   b. Topical calcineurin inhibitors (eg, tacrolimus, pimecrolimus) have been reported to improve erythema and pruritus [11,12].
   c. Topical bleaching agents (hydroquinone 4.0% cream) alone or in combination with topical tretinoin and steroids have been used to treat postinflammatory hyperpigmentation in the setting of inactive disease. The efficacy of this intervention is modest and depends on skin type and depth of pigmentation.

Topical Care for Nonintact Skin

When appropriate, superficial or deep tissue culture should be obtained to test for bacterial, viral, fungal, or mycobacterial infection in eroded, ulcerated, or suspicious skin lesions. The differential diagnosis for noninfectious skin lesions includes vasculitis, recurrent malignancy, GVHD, hypersensitivity or drug reactions, dermatitis, and primary skin cancer.

In denuded skin, wound dressings maintain a moist environment that enhances repair of the epithelium, lysis of necrotic tissue, and phagocytosis of necrotic debris. Protective films may be applied to prevent breakdown of fragile or compromised but nonulcerated skin. If indicated, topical antimicrobials such as mupirocin ointment or silver-containing products may be useful.

Recalcitrant wounds or major wounds are best treated in consultation with a plastic surgeon. Wounds that have been slow to heal may be treated with hyaluronic acid products, collagen products, or fibroblast and keratinocyte products. Nonhealing wounds that involve the dermis may benefit from platelet-derived growth factor products. Hyperbaric oxygen therapy has been used to treat hypoxic wounds [13].

Compression therapy may be indicated to facilitate drainage of periwound edema. The use of diuretics can provide local benefit in some instances, but these benefits must be weighed against the risk of adverse effects on renal function in patients who receive concomitant treatment with nephrotoxic immunosuppressive medications.

For specific dispensing information, please see www.asbmt.org/GvHDForms.

Table 4. *Ancillary Therapy and Supportive Care Recommendations for Mouth and Oral Cavity GVHD*

Target Tissue	Rating
Mild/moderate* mucosal disease	
Localized application of high potency topical corticosteroids (fluocinonide gel 0.05%)	AIIa
Generalized application of upper mid-strength topical corticosteroids (dexamethasone 0.5 mg/5 mL, prednisolone 15 mg/5 mL, triamcinolone 0.1%)	AIIa
Topical analgesics (viscous lidocaine, 2%, Kaopectate-Benadryl-Lidocaine oral rinse, 1:1:1, diclonine hydrochloride 1%)	AIII
Localized application of upper mid-strength topical corticosteroids (clobetasol gel 0.05% or betamethasone dipropionate gel 0.05%)	AIIb
Topical application of tacrolimus 0.1% ointment	BIIa
Intralesional therapy with high-potency steroids for refractory lesions (Kenalog 40, 0.3-0.4 mL for ~1.0-cm^2 lesion)	BIII
Topical application of cyclosporine rinses (requires compounding by pharmacist)	CIIa/Ib
Oral phototherapy (psoralen–UV-A, UV-B, or narrow band UV-B but none is widely available)	CIIa
Topical application of azathioprine rinses (requires compounding by pharmacist)	CIII
Salivary gland disease	
Home fluoride therapy (neutral sodium fluoride)	AIb
Frequent water sipping and saliva substitutes	AIII
Salivary stimulants (sugar-free gum, sugar-free candy)	AIII
Mild dentrifice use	AIII
Sialogogues	
Cevimeline	BIb
Pilocarpine	BIb/IIa
Sclerotic perioral and intraoral diseases	
Intralesional corticosteroid therapy	CIII
Pediatric considerations	
Oral manifestations in children generally respond well to dexamethasone rinses	
Prolonged use of ultrahigh potency steroids should be avoided in the very young child because of the potential for greater systemic effects	
There is limited experience, and dosing is not established for the use of sialogogue therapy in children	
Specific approaches to help parents assist children with topical oral therapies may improve pediatric compliance	

*Definitions of severity are provided in the diagnosis and scoring document [3].

MOUTH AND ORAL CAVITY

See Table 4. Chronic GVHD involving the mouth and oral mucosa has 3 components: mucosal involvement, salivary gland involvement, and sclerotic involvement of the mouth and surrounding tissues. Oral

chronic GVHD can cause pain, odynophagia, taste impairment, dryness, and decreased range of motion. Infection with herpes simplex virus (HSV), human papilloma virus, *Candida*, and other fungal organisms should be ruled out before initiating any form of therapy. When clinically indicated, viral and bacterial cultures and biopsies should be performed.

Patients with persistent or new oral lesions that occur >3 years after HCT should be evaluated for secondary cancer involving the oral cavity (especially squamous cell carcinoma). These cancers generally begin as leukoplakia, which may be misdiagnosed as chronic GVHD. Leukoplakia must be biopsied periodically to rule out progression to frank malignancy. When leukoplakia is caused by chronic GVHD, aggressive treatment with clobetasol usually results in resolution or considerable softening of the "white lesion" but persistence or worsening of the lesion requires biopsy. Suspicious lesions of the vermillion border of the lip also require biopsy and culture.

Ancillary treatment may provide greater local benefits than systemic therapy alone. When the oral cavity is the only site of chronic GVHD activity, with mild to moderate severity, ancillary treatment might suffice to control the disease in the absence of systemic therapy. However, systemic therapy should be added early in the treatment of severe oral cavity GVHD (eg, skin sclerosis) and whenever isolated oral cavity GVHD fails to respond to ancillary measures.

Oral Cavity and Vermillion Border Chronic GVHD

The mainstay of therapy for localized and symptomatic disease is the application of a high potency corticosteroid gel (fluocinonide, clobetasol, or betamethasone dipropionate) [14-16]. It is also appropriate to treat asymptomatic pseudomembranous ulcers to reestablish integrity of the mucosal barrier. The application of tacrolimus ointment is an alternative to locally applied corticosteroids [17,18]. Vaseline-based ointments such as topical tacrolimus are generally less effective in the mouth than are alcohol-based corticosteroid gels but are preferable for the treatment of "chapped lips" caused by GVHD, because high potency steroids cause irreversible atrophy when applied to the vermillion border of the lips. Discrete lesions that fail to respond to topical therapy may resolve within 3-4 weeks after weekly intralesional injections of triamcinolone [14].

The mainstay of therapy for more generalized and symptomatic disease is corticosteroid rinses directed at the entire oral cavity. Dexamethasone and other corticosteroid rinse formulations such as prednisolone or triamcinolone are held and swished in the mouth for 4-6 minutes and then expelled without swallowing. Treatments are administered 4-6 times per day [14,16]. Alternative noncorticosteroid rinse formulations of cyclosporine or azathioprine may be effective in refractory cases [19]. Systemic treatment with azathioprine has been associated with an increased risk of secondary malignancy. For this reason, patient should be counseled about the risk of oral cancer, and the duration of treatment with azathioprine rinses should generally not exceed 12 months. Associations between other topical immunosuppressants and secondary cancers have been less well studied.

All patients should be counseled about the relatively frequent side effect of oral candidiasis, which can be managed with appropriate prophylaxis or treatment. Patients should also be warned about systemic effects that can result from topical therapy with highly potent steroids.

Topical analgesia is helpful when symptomatic mucosal GVHD impairs nutrition or communication. Viscous lidocaine is often effective.

Salivary Gland Chronic GVHD

Patients with salivary gland involvement most frequently report dry mouth and variable oral sensitivities to hot, cold, spicy, and acidic food, mint (such as toothpaste), and carbonated beverages [14,20,21]. They may also develop mucoceles, which are recognized as painless blisters on the palate and inside the lower lip [22,23].

Ancillary care for dry mouth may include frequent water sipping, the use of salivary stimulants (sugar-free gum and candy), oral moisturizing agents, and saliva substitutes. Symptomatic patients should avoid mint-flavored dentifrices and whitening products. The milder flavored dentifrices marketed for children are often tolerated. Caries can be prevented by home fluoride treatments before sleep. Even in patients without subjective oral dryness, mild salivary gland dysfunction can increase the risk of tooth decay, and topical fluorides should be offered as a decay-prevention strategy [14,24]. If possible, avoidance of xerogenic medications such as tricyclic antidepressants, specific serotonin reuptake inhibitors, antihistamines, and narcotic analgesia can substantially alleviate symptoms of dry mouth. Sialogogue therapy with cholinergic agonists (cevimeline, pilocarpine) may produce a significant enhancement of salivary secretion and may be offered in the absence of contraindications (eg, glaucoma, heart disease, or asthma) [25,26].

Superficial mucoceles require no treatment. Symptomatic mucoceles should be distinguished from herpetic lesions and may respond to topical steroids or topical analgesics. Deep mucoceles require surgical excision, particularly when they cause symptoms.

Sclerotic Manifestations of Chronic GVHD

Topical therapy alone is insufficient to treat sclerosis of the perioral skin and surrounding tissues

Table 5. *Ancillary Therapy and Supportive Care Recommendations for Eye GVHD*

Therapy	Indication	Rating
Topical	Mild*	
	Artificial Tears, preservative free	AIb
	Viscous ointment at bedtime, viscous tears during the day	BIb
	Moderate/severe*	
	Cyclosporine eye drops	CIb
	Topical steroid drops	BIIIa
	Lacriserts for patients who use Artificial Tears more frequently than hourly	CIb
Oral	Moderate/severe*	
	Cevimeline	CIb
	Pilocarpine	CIb
	Doxycycline	CIII
Surgical	Moderate/severe*	
	Punctal occlusion (temporary or permanent occlusion, using silicone plugs or thermal cautery)	BIb
	Superficial debridement of filamentary keratitis	CIII
	Partial tarsorrhaphy	CIIb
Eyewear/environmental strategy	Moderate/severe*	
	Occlusive eye wear (www.dryeyepain.com; www.panoptx.com)	BIII
	Lid care/warm compress/humidified environment	CIII
	Bandage contact lens (used with extreme caution)	
Treatment not widely available	Moderate/severe*	
	Autologous serum eye drops	CIb
	Gas-permeable contact lens (Boston scleral lens prosthesis, www.bostonsight.org)	CIIa
Pediatric considerations		
Although severe ocular sicca is uncommon in children with chronic GVHD, measured tear production is decreased, and surveillance for keratoconjunctivitis sicca is necessary		
Ocular sicca generally responds to ancillary measures in conjunction with systemic immunosuppression		
Experience is limited, and dosing is not established for many of the topical and oral medications for ocular GVHD		

*Definitions of severity follow the diagnosis and scoring report [3].

caused by chronic GVHD. In this situation, systemic treatment is required. Adjunctive intralesional steroid injections may be helpful, but long-term therapy is often required to maintain the response. Stretching exercises to increase range of motion of the mouth may be helpful.

Routine Dental Treatment

No consensus could be reached regarding the advisability of routine dental cleanings or the need for endocarditis prophylaxis in patients with chronic GVHD. When dental treatment is required, the American Heart Association's guidelines for prevention of bacterial endocarditis provide recommendations with regard to antibiotic prophylaxis, but no recommendations for patients with chronic GVHD have been published, and the need for routine prophylaxis in patients with chronic GVHD is controversial [27]. These guidelines may be appropriate for patients with delayed immune reconstitution, persistently low counts (especially absolute neutrophil count), or a history of infectious complications after HCT. Extended antibiotic therapy based on the dental disease, the type of treatment, and the patient's risk for infection should be determined by the treating dental physician or oral surgeon in consultation with the transplantation center.

For specific dispensing information, please see www.asbmt.org/GvHDForms.

EYES

See Table 5. The clinical spectrum of chronic ocular GVHD includes acute conjunctival inflammation, pseudomembranous and cicatricial conjunctivitides, and keratoconjunctivitis sicca (KCS) syndrome. This report will focus on the dry eye syndrome (KCS). KCS often accompanies chronic GVHD activity in other organs and may be a prominent disease manifestation; conversely, dry eyes may occasionally be the only manifestation of chronic GVHD [28]. The diagnosis of KCS is made by the presence of appropriate symptoms, tear production averaging $\leq$5 mm (Schirmer test), and clinical signs of keratitis. Although ocular symptoms and external examination can be ascertained from a clinic visit, a slit lamp examination by an ophthalmologist is generally required to make the diagnosis of KCS. In all cases, infectious keratitis must be ruled out. Most symptomatic treatments for ocular chronic GVHD are aimed at relief of dry eyes.

Symptoms include burning, irritation, pain, foreign body sensation, blurred vision, photophobia, and, paradoxically, excessive tearing [29]. Other causes of dry eyes need to be considered, such as medications

with anticholinergic side effects (antihypertensives, antidepressants, psychotropics, antihistamines, decongestants) and previous treatments (eg, total body irradiation, chemotherapy, history of autologous HCT).

Aqueous tear deficiency/lacrimal gland dysfunction may fluctuate during systemic GVHD. Although systemic immunosuppressive therapies for chronic GVHD generally do not lead to improvement in Schirmer scores (especially if lacrimal gland dysfunction has been long term), they can improve overall symptoms of ocular GVHD.

If possible, an ophthalmologist who is knowledgeable about HCT and GVHD should be involved to coordinate care in a multidisciplinary fashion. Ancillary and supportive care for the eye focuses on increasing ocular surface moisture (by lubrication and decreasing tear evaporation and tear drainage from the surface of the eye) and on decreasing ocular surface inflammation.

Lubrication

For lubrication, the range of adjunctive measures includes the use of preservative-free artificial tears to coat the ocular surface, thereby minimizing superficial punctuate keratopathy (dry spots on the cornea), decreasing ocular symptoms, and improving quality of vision. Because patients may tolerate certain formulations better than others, they should be encouraged to test different brands to identify one that provides the most benefit.

For patients who may require application of artificial tears more than once every hour, slowly dissolving 5-mg pellets of hydroxypropyl methylcellulose may provide more convenience [30]. Lacrisert is available by prescription and is inserted once or twice daily into the inferior cul-de-sac of the eye but may produce a constant foreign body sensation. Oral medications may be used to increase lubrication by stimulating aqueous tear flow with selective muscarinic agonists such as cevimeline or pilocarpine [31]. These have been shown to improve sicca symptoms in patients with Sjögren syndrome, but drug interactions and toxicities must be reviewed, because contraindications include glaucoma, heart disease, and asthma.

Control of Evaporation

To decrease evaporation, patients should be encouraged to use warm compresses and lid care to maximize the output of the meibomian glands that produce the outer oil layer of the tear film, which protects against evaporation. Avoidance of low humidity and use of eye protection (eg, moisture chamber goggles) may also help to decrease evaporation [32]. Doxycycline can be used to treat rosacea blepharitis/meibomitis, thereby decreasing inflammation on the lids and establishing an optimal oil layer to decrease evaporation [33]. For refractory cases, surgery to decrease the exposed surface area (tarsorrhaphy) may be necessary [34]. Scleral lenses may also be beneficial in severe cases, but this treatment is available in only a limited number of centers [35].

Control of Drainage

To decrease drainage from the surface of the eye, temporary or permanent occlusion of the tear-duct puncta may provide additional benefit for patients with severe ocular sicca syndrome (<5 mm tear wetting) [36-38]. Permanent punctal occlusion (by thermal cauterization) may be necessary because the silicone plugs used for temporary occlusion fall out repeatedly. Repeated thermal cautery may be needed if puncta reopen.

Decreasing Ocular Surface Inflammation

To decrease ocular surface inflammation, judicious use of topical steroids may be necessary. In general, this type of treatment should be reserved for the control of ocular GVHD exacerbation when systemic immunosuppression is being tapered [39]. Topical steroids may also benefit patients with cicatricial conjunctivitis [40]. Pulsed topical steroids should be carefully supervised by an ophthalmologist, because steroid-related complications include increased intraocular pressure, cataract formation, and silent infectious keratitis. Topical cyclosporine can be prescribed to control immune responses at the ocular surface [41]. The benefit of topical cyclosporine on tear function in patients with GVHD has not been fully elucidated, but this type of treatment increases Schirmer scores and decreases surface apoptosis in patients with other dry eye conditions. Ocular surface inflammation may also be decreased with autologous serum, but this treatment is available in only a limited number of centers [42,43].

For specific dispensing information, please see www.asbmt.org/GvHDForms.

VULVA AND VAGINAL MUCOSA

See Table 6. Chronic GVHD involving the vulva or vagina has been reported in approximately 3% of bone marrow recipients and 15% of peripheral blood recipients [44]. The diagnosis of vulvovaginal GVHD relies on symptoms and physical findings. Histologic confirmation is strongly recommended in the absence of diagnostic manifestations of chronic GVHD in other organs. Estrogen deficiency and infections (human papilloma virus, HSV, yeast, bacteria, or other recognized gynecologic pathogens) must be ruled out at the time of initial diagnosis and periodically during management of vulvar or vaginal GVHD.

Table 6. *Ancillary Therapy and Supportive Care Recommendations for Vulvar and Vaginal GVHD*

Type of Intervention	Rating
Vulvar discomfort	
Avoid mechanical and chemical irritants (eg, soap and feminine wash products)	BIII
Clean genital area with warm water, allow air circulation, and wipe front to back	BIII
Sparing use of simple emollients to vulva (not vagina)	BIII
Water-based lubricants	BIII
Vulvovaginal symptoms and low estrogen status	
Topical estrogen with/without dilator (dilator necessary only for vaginal symptoms)	BIII
Topical therapy for vulvovaginal GVHD	
High and ultrahigh potency corticosteroids	
Clobetasol gel 0.05% (vagina)	BIIb
Betamethasone dipropionate augmented gel (vagina) or ointment (vulva)	BIII
Tacrolimus ointment 0.1% (vulva)	BIIb
Surgical therapy	
Surgical lysis with or without vaginal reconstruction followed by 6 mo of dilator therapy may be necessary for treatment of extensive synechiae and complete obliteration of the vaginal canal	BIII
Pediatric considerations	
Vulvar or vaginal GVHD needs to be considered as soon as physical development has progressed beyond thelarche and into pubarche; vulvovaginal GVHD has been observed infrequently in prepubertal girls	
Evaluation by an adolescent gynecologic practitioner is recommended when a diagnosis of vulvovaginal GVHD is being considered	

Chronic GVHD of the vulva and vagina presents with abnormalities of the mucosa or manifestations of sclerotic changes. Symptoms may include dysuria, dryness, tenderness to touch, and dyspareunia. Mild chronic GVHD of the vulva or vagina may occasionally be asymptomatic and detected only by examination. Physical findings include erythematous patches (mucositis), retiform leukokeratosis (lichen planus-like lesions), vestibular tenderness, and, less often, excoriations and ulcers. Eventually, sclerosis of vulvar and vaginal tissues can lead to architectural changes such as agglutination of the clitoral hood, narrowing of the introitus, and shortening of the vaginal canal. Although most patients with vulvar or vaginal GVHD have involvement of the mouth or other sites, vulvovaginal manifestations may sometimes be the only sign of chronic GVHD [45,46].

Symptomatic patients should be evaluated and followed by a gynecologist with experience in GVHD and, if not available, by practitioners with experience in lichen planus of the genitalia.

General Hygiene

Irrespective of the underlying cause, the following hygiene measures are recommended for the prevention or alleviation of vulvar or vaginal symptoms. Mechanical and chemical irritants should be avoided. The genital area is best cleaned with warm water rather than with soap or feminine wash products. The area may be air-dried and patients should be counseled to wipe in a front-to-back direction. A small amount of emollients or lanolin cream applied to the external genitalia and not into the vagina may provide relief from itching and irritation, provided that abnormal discharge (infection) is not also present. Replens or other bacteriostatic gels may be used in the vagina for comfort. Replens adheres to the vaginal wall and is intended to have a longer lasting effect than bacteriostatic water-soluble gels.

Symptomatic Low Estrogen States

If vulvovaginal symptoms and signs are accompanied by low estradiol levels, topical estrogen therapy with or without the use of a vaginal dilator should be initiated unless there are absolute contraindications such as increased risk of breast cancer or cardiovascular events. Symptoms caused by gonadal failure generally dissipate during treatment with topical estrogen. Although there is anecdotal evidence that estrogen replacement (systemic or topical) is an effective adjunctive therapy for vulvar or vaginal GVHD, prospective controlled studies are needed.

Vulvovaginal GVHD

When the vulvovaginal region represents the only clinical manifestation of chronic GVHD activity, topical immunosuppressive agents may constitute an adequate primary therapy for controlling mild clinical manifestations. Application of ultrahigh potency corticosteroid is the mainstay of therapy, although topical calcineurin ointments have also been used in patients with chronic GVHD and in other patients with erosive vulvovaginal lichen planus disease [47-49]. Patients may develop candidiasis or recurrence of HSV or human papilloma virus during immunosuppressive therapy and must be counseled to monitor for symptoms.

Systemic immunosuppression should be used in patients at high risk of nonrelapse mortality (thrombocytopenia or requirement for systemic steroids at time of diagnosis). Systemic immunosuppressive therapy is also indicated for vulvovaginal GVHD that

progresses or fails to improve after treatment with local measures. Increased systemic immunosuppressive therapy or addition of local therapy is indicated if vulvovaginal GVHD develops during systemic immunosuppressive treatment.

Sclerotic features of vaginal GVHD should be treated aggressively with topical corticosteroids and dilators. Surgical lysis with or without vaginal reconstruction may be necessary for patients with extensive synechiae and complete obliteration of the vagina canal. Subsequent topical treatment with calcineurin inhibitors has been used successfully in some cases.

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GASTROINTESTINAL TRACT AND LIVER

See Table 7. Gastrointestinal symptoms occur frequently in patients with chronic GVHD. Dysphagia, odynophagia, heartburn, anorexia, nausea, vomiting, abdominal pain, cramping, diarrhea, weight loss, and malnutrition may occur. It is usually unclear whether these symptoms are directly related to chronic GVHD, acute GVHD, or another etiology, which makes it important to confirm the diagnosis of chronic GVHD before beginning treatment [50,51].

Odynophagia and Dysphagia

Lubrication can ease discomfort due to xerostomia. Other possible causes of odynophagia or dysphagia include esophageal webs, rings, strictures, dysmotility, or nonchronic GVHD diagnoses such as pill esophagitis, radiation esophagitis, and fibrosis. Endoscopy is usually needed to exclude or confirm these diagnoses. Esophageal dilation may be helpful in patients with documented webs or strictures, but this procedure can cause perforation and should be performed by an experienced gastroenterologist.

Diarrhea

Patients who present with diarrhea should have a standard evaluation including cultures, *Clostridium difficile* toxin screen, cytomegalovirus (CMV) cultures, endoscopy (because CMV can cause colitis without antigenemia), and consideration of an alternative diagnosis such as enzyme deficiency, bacterial overgrowth, and medication side effects. A careful history may suggest secondary intestinal disaccharidase deficiency, lactose intolerance, or pancreatic insufficiency. Pancreatic enzyme supplementation may be helpful in patients with diarrhea and malabsorption. Antibiotic-related suppression or overgrowth of intestinal flora may cause diarrhea. Certain medications such as magnesium oxide and mycophenolate mofetil may also cause diarrhea. The use of magnesium with protein may decrease the risk of diarrhea, because the mineral is bound to a soy protein, thereby eliminating the laxative effects that occur frequently with the use of other magnesium supplements.

Table 7. *Ancillary Therapy and Supportive Care Recommendations for Gastrointestinal/Liver GVHD*

Type of Intervention	Rating
Esophageal dilation for webs or stricture	**BIII**
Dietary modifications	**BIII**
Pancreatic enzyme replacement	**BIIa**
Ursodeoxycholic acid	**BIIa**
Lactase tablets or lactase-containing dairy products	**BIII**
Pediatric considerations	
No substantive differences	

Abnormal Liver Function Tests

Imaging studies should be obtained if there is suspicion of gallbladder disease or to exclude liver abscess, infiltration, or other morphologic abnormality. If iron overload could be contributing to liver function abnormalities, additional radiographic and laboratory studies should be performed. Use of ursodeoxycholic acid can help to improve biochemical abnormalities and perhaps pruritus in some patients with hepatic chronic GVHD. Liver transplantation has been used in a small number of patients with advanced liver chronic GVHD, but this procedure is not a viable treatment option in most patients [52].

Weight Loss

Weight loss in patients with extensive chronic GVHD may also be caused by increased action of glucagon and norepinephrine, resulting in an increase in resting energy expenditure and alterations in fat and carbohydrate oxidation rates [53]. Nutritional support is very important because >40% of patients with chronic GVHD are malnourished [50]. The input of a nutritionist can be very helpful in addressing weight loss, because some patients will need total parenteral nutrition or tube feedings. A multidisciplinary team (gastroenterologist, nutritionist, oncologist, etc) may help to maximize the benefits of therapy.

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LUNG

See Table 8. The currently recognized noninfectious pulmonary manifestations in patients with chronic GVHD are HCT-related airflow decline and bronchiolitis obliterans, with the latter representing a severe form of airflow obstruction that is the only diagnostic manifestation of pulmonary chronic GVHD [54]. Chronic GVHD of the lung can cause dyspnea, wheezing, coughing, air trapping, bronchiectasis, pneumothorax, pneumomediastinum, subcutane-

Table 8. *Ancillary Therapy and Supportive Care Recommendations for Lung GVHD*

Type of Intervention	Rating
Inhaled corticosteroids and bronchodilators	**CIb**
Prophylactic intravenous immunoglobulin	**DIa**
Pulmonary rehabilitation	**CIII**
Supplementary oxygen	**AIII**
Pediatric considerations	
Formal spirometry, lung volumes, and diffusing capacity are not measurable in children <7 y of age, but negative plethysmography is an option	
Actual measured pulmonary function test values must be carefully considered in pediatric patients because predicted normal values vary with age, weight, and height; therefore, percent predicted values might spuriously show serial decreases over time without substantive decreases in absolute values	

ous emphysema, microbial colonization or infection, and obstructive or restrictive changes on pulmonary function tests (PFTs). Silent pulmonary aspiration disease must be considered in patients with chronic GVHD and airflow limitation, especially in those who have chronic postnasal drip, recurrent sinus infections, or gastroesophageal reflux disease [54,55].

Bronchodilators, inhaled corticosteroids [56], and pulmonary rehabilitation programs may provide benefit for patients with pulmonary chronic GVHD. Prophylactic immunoglobulin infusions do not prevent bronchiolitis obliterans, and their use is not recommended for this purpose [57]. If the need for supplemental oxygen is documented (saturation of oxyhemoglobin [SpO_2] <87% while breathing room air), then the amount of oxygen supplementation should be titrated with the use a 6-minute walk test. Standard 6-minute walk protocols should be conducted according to guidelines of the American Thoracic Society [58]. Interventions such as inhaled cyclosporine, amphotericin, or tobramycin, rotating empiric antibiotics pioneered in lung transplantation, and management of cystic fibrosis have not been rigorously tested in patients with chronic GVHD.

Because patients may have subclinical changes in pulmonary function before a diagnosis of chronic GVHD, some experts have advocated the routine use of PFTs to monitor for changes [54,59,60]. No studies have been conducted to determine the optimal intervals for monitoring PFTs after HCT. Recent studies have indicated that decreased lung function during the first year after HCT is significantly associated with a higher mortality risk [54]. In addition, changes in lung function at 100 days after HCT do not reflect the changes that may occur between day 100 and 1 year, when immunosuppressive therapy is often weaned and pulmonary complications such as airflow obstruction, bronchiolitis obliterans, and cryptogenic organizing pneumonia (also known as bronchiolitis obliterans with organizing pneumonia) are most likely to occur [55,61]. Studies have not been done to assess the role of bronchoscopy or chest imaging in monitoring for pulmonary complications after HCT [62].

Figure 1 presents 1 possible algorithm for pulmonary monitoring and intervention after HCT. Full PFTs, which include spirometry, lung volumes, and diffusing capacity of the lung for carbon monoxide (DL_{CO}) are obtained before HCT and at 1 year afterward. Screening with spirometry and DL_{CO} measure-

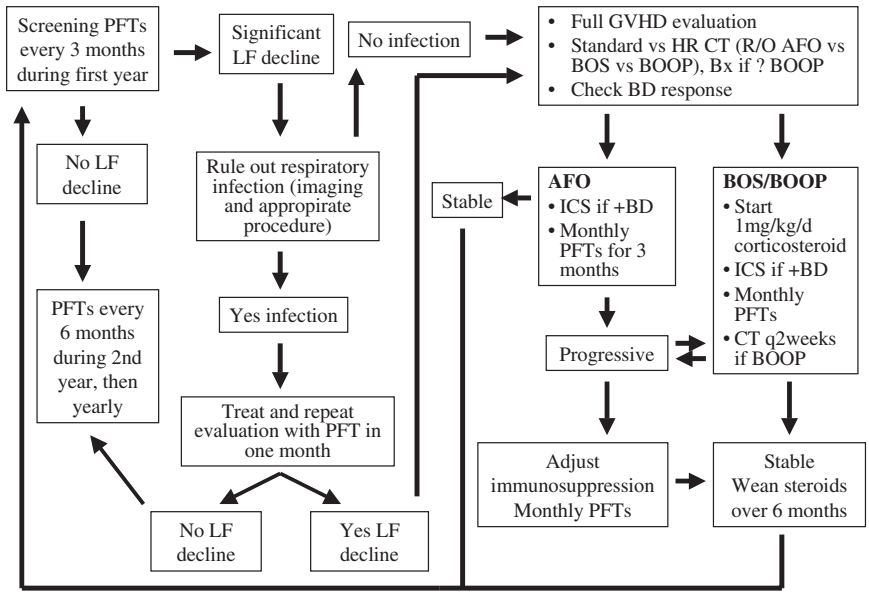

Figure 1. Possible algorithm for pulmonary monitoring after HCT. AFO, airflow obstruction; BD, bronchodilators; BOS, bronchiolitis obliterans syndrome; BOOP, bronchiolitis obliterans with organizing pneumonia; Bx, biopsy; CT, computed tomography scan; HR, high resolution; ICS, inhaled corticosteroids; LF, lung function; PFTs, pulmonary function tests; R/O, rule out.

ments alone can be used more frequently. If the lung function staging index[3] increases by 1 category in comparison with the previous study, it is appropriate to perform a full PFT followed by appropriate additional studies. All pulmonary function testing should be performed according to criteria of the American Thoracic Society [63] and interpretation of results should be conducted as summarized by Chien et al [60]. All reference values should be calculated according to the equations of Crapo et al [64] and Hsu et al [65] for adults and children. The DL_{CO} should be corrected for hemoglobin but not for alveolar volume. Lung volumes should be measured with body plethysmography and not with a gas-based method.

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HEMATOPOIETIC SYSTEM

See Table 9. Cytopenias may be caused by stromal damage, graft failure, drug toxicity, infection, relapse of underlying disease, CMV infection, hemolysis, anemia of chronic disease, and autoimmune processes, including GVHD [66-69]. Intravenous immunoglobulin may be effective in certain cytopenias that have not improved after steroid treatment [67,69]. Growth factor use has not been formally evaluated in patients with chronic GVHD and persistent cytopenias. Thrombocytopenia at the time of diagnosis of chronic GVHD is associated with poor prognosis [51,70] but may also be caused by autoantibodies that would respond to treatment with steroids or rituximab. Eosinophilia can occur with acute or chronic GVHD [71,72]. In patients with chronic GVHD, eosinophilia has been associated with increased serum levels of interleukin 5 [73] and can herald or represent disease activity [74].

NEUROLOGIC SYSTEM

See Table 10. Chronic GVHD of the nervous system is rare but can present as polyneuropathy, myositis, and myasthenia [75]. Symptoms may include muscle weakness and wasting, pain, burning, dysesthesias, and paresthesias. Less clearly associated with chronic GVHD are central nervous system manifestations such as cerebral angiitis and vasculitis or encephalitis-like disease [76,77].

Table 9. *Ancillary Therapy and Supportive Care Recommendations for Hematopoietic GVHD**

Type of Intervention	Rating
Growth factors (G-CSF, GM-CSF, erythropoietin)	**CIII**
Immunoglobulin for cytopenias	**CIII**
Pediatric considerations	
No substantive differences	

*G-CSF indicates granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor.

Table 10. *Ancillary Therapy and Supportive Care Recommendations for Neurologic Syndromes of GVHD**

Type of Intervention	Rating
Neuropathies	
Tricyclic antidepressants	**BIIb**
SSRIs	**CIIb**
Anticonvulsants	**BIb**
Neuropathies/myopathies/CNS disease	
Rehabilitation medicine (PT/OT)	**CIII**
Plasmapheresis for TTP	**BIIb**
IVIg	**BIIb**
Pediatric considerations	
Drugs of the SSRI antidepressant class should generally be used under expert supervision because of the increased risk of suicidal tendencies associated with their use in children	
Gabapentin may be used with success for treating extremity dysesthesias or muscle cramps	

*SSRIs indicates selective serotonin reuptake inhibitors; PT/OT, physical therapy/occupational therapy; TTP, thrombotic thrombocytopenic purpura; IVIg, intravenous immunoglobulin.

Neuropathy and Myopathy

Painful neuropathy and myopathy can occur in patients with chronic GVHD [75]. Consideration of chronic inflammatory demyelinating polyneuropathy may require cerebrospinal fluid examination, electromyelographic studies, and sural nerve biopsy if symptoms present without other evidence of chronic GVHD [75,78]. Neuropathic pain can occur in a dermatomal distribution in the absence of rash during the prodromal phase of varicella zoster virus (VZV) reactivation. Specific interventions for painful peripheral neuropathies may include the use of tricyclic antidepressants [79], selective serotonin reuptake inhibitors [80], and anticonvulsants [81]. Narcotic analgesics are poorly effective as a solitary approach for relieving neuropathic pain, but they may provide some relief and can be an important adjunct to treatment [82]. Medications may need to be titrated up every 1-2 weeks until symptoms are adequately controlled. Rehabilitation medicine consultation with physical and occupational therapists should be considered for all patients who have a decreased ability to perform activities of daily living or impaired quality of life because of pain or muscle weakness. Physical therapy evaluation may be needed every 1-3 months to assess response of muscle weakness and range of motion.

Myasthenia Gravis and Polymyositis

Myasthenia gravis may occur in patients when immunosuppressive medications are being tapered. The diagnosis is suggested by the syndrome of ptosis, extraocular muscle weakness, and proximal limb and

facial weakness in the presence of antiacetylcholine receptor antibodies [83].

Polymyositis can present with proximal muscle weakness that is often painful and associated with an increased serum concentration of creatinine phosphokinase and aldolase [84]. Isolated polymyositis as the sole manifestation of chronic GVHD occurs rarely, and muscle biopsy may be required to establish the diagnosis [85,86].

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IMMUNOLOGIC AND INFECTIOUS DISEASES

See Table 11. Infection is often the cause or a contributing factor when patients with chronic GVHD die. The immune defect in chronic GVHD is broad, encompassing macrophage function, antibody production, and T-cell function. Prevention, early diagnosis, and prompt treatment of infections are essential to the supportive care of patients with chronic GVHD. Most recommendations, however, are based on expert opinion and not on controlled trials [59,87-89]. Recommendations supported by evidence are typically based on results from studies with patients who had conditions other than chronic GVHD. Comprehensive guidelines for the prevention of opportunistic infections after HCT have been published in collaboration by the Center for Disease Control and Prevention, the Infectious Disease Society of America, and the American Society of Blood and Marrow Transplantation [90].

Antibacterial Prophylaxis

All patients with chronic GVHD are considered at risk for infection with encapsulated bacteria, in particular *Streptococcus pneumoniae*, but also *Haemophilus influenzae*, and *Neisseria meningitides*. Prophylactic antibiotics should be given to all patients with chronic GVHD as long as systemic immunosuppressive treatment is being administered [91,92]. Penicillin V K is the prophylactic agent of choice when the frequency of penicillin-resistant *S pneumoniae* is low. Alternatives include azithromycin or other macrolides and newer generation quinolones, although drug interactions can cause problems. Daily use of trimethoprim-sulfamethoxazole has also been used for this indication, but its efficacy has not been demonstrated.

Antibiotic prophylaxis before dental extractions and other invasive procedures in patients with chronic GVHD has not been studied, and consensus on this subject has not been reached [59].

Vaccinations

Although no studies have evaluated the degree of protection provided by pneumococcal (polyvalent polysaccharide or heptavalent), *H influenzae* type b conjugate, or influenza vaccination in patients with chronic GVHD, most experts advocate their use because the risk of adverse outcomes with vaccination is

Table 11. *Ancillary Therapy and Supportive Care Recommendations for Immunologic and Infectious Consequences of GVHD**

Interventions	Grade
Antibacterial prophylaxis	
Antibiotic prophylaxis for encapsulated organisms	**BIIb**
Pneumococcal vaccine	**BIIb**
Hib vaccine	**BIIb**
IVIg routinely following allogeneic HCT	**D**
IVIg in patients with chronic GVHD, hypogammaglobulinemia and repeated sinopulmonary infections	**CIII**
Antibiotic prophylaxis before dental extractions and other invasive procedures	**CIII**
Antifungal prophylaxis	
Prophylaxis for *Candida* infection during chronic GVHD	**CIII**
Prophylaxis with agents with activity against mould during chronic GVHD	**CIII**
***Pneumocystis* prophylaxis**	**AIb**
Antiviral prophylaxis	
HSV prophylaxis	**D**
VZV prophylaxis	**CIa**
Influenza vaccination	**BIII**
Early empirical treatment with oseltamivir during influenza outbreaks	**CIII**
Pediatric considerations	
Children undergoing HCT have frequently missed routine childhood immunizations; review of immunization history and patient-specific vaccination is indicated	
Heptavalent-conjugated pneumococcal vaccine is recommended at 12 and 14 mo after HCT for patients ≤5 y of age; it is also recommended that children 2-5 y of age receive 1 dose of the 23-valent pneumococcal vaccine 2 mo after the last dose of the heptavalent-conjugated vaccine	

*Hib indicates *Haemophilus influenzae* type b conjugate, IVIg, intravenous immunoglobulin; HSV, herpes simplex virus; VZV, varicella zoster virus.

low [93-95]. No live viruses, including the new live attenuated influenza vaccine and measles-mumps-rubella vaccine, should be given. Household contacts should not be given oral polio vaccine.

Intravenous Immunoglobulin

Universal administration of intravenous immunoglobulin (IVIg) after HCT has not been shown to confer clinical benefit and should be avoided [96,97]. In patients with hypogammaglobulinemia caused by other disorders, administration of IVIg to maintain IgG levels >400 mg/dL has been associated with a decreased incidence of severe bacterial infections [98-100]. IVIg may be considered for patients >90 days after HCT who have recurrent sinopulmonary infections and serum IgG levels <400 mg/dL. Some experts recommend monitoring IgG levels and administering IVIg routinely in chronic GVHD, but there are no data demonstrating that this approach improves outcomes.

Antifungal Prophylaxis

There is no evidence to support the use of antifungal prophylaxis >75 days after HCT. However, invasive mold infections are a significant concern in patients who receive immunosuppressive treatment for chronic GVHD. Some centers prescribe prophylactic mold-active agents for patients with chronic GVHD, but this approach remains investigational because the benefits and risks are unknown [101].

Pneumocystis Prophylaxis

Pneumocystis pneumonia >6 months after HCT is strongly associated with chronic GVHD. All patients who receive immunosuppression after allogeneic HCT should receive *Pneumocystis* prophylaxis [102-104]. It is unknown how long prophylaxis should be continued after stopping immunosuppression, and practices vary widely across centers. Agents used for *Pneumocystis* prophylaxis include trimethoprim-sulfamethoxazole, pentamidine, dapsone, and atovaquone. Trimethoprim-sulfamethoxazole also provides prophylaxis against toxoplasmosis and nocardia.

Antiviral Prophylaxis

Approximately 30-60% of patients develop an episode of zoster during the first year after discontinuing post-transplant prophylaxis [105]. Some experts use long-term antiviral prophylaxis to prevent recurrent HSV and VZV infection among HCT recipients with severe, long-term immunodeficiency [106-108], but current evidence does not support routine administration of antiviral prophylaxis for HSV in patients with chronic GVHD. If VZV-seronegative patients with chronic GVHD are exposed to varicella (primary or postvaccination illness), VZV Ig should be given within 96 hours.

CMV disease after day 100 has become more common. The best strategy to monitor and treat CMV after day +100 has not been defined. Patients with active GVHD [109], a history of CMV reactivation during the first 3 months, and lymphopenia are at higher risk of CMV reactivation and death. Some centers continue to monitor for CMV infection after day 100 by pp65 antigenemia or polymerase chain reaction (PCR) tests, followed by preemptive therapy, based on the individual risk as determined by donor and recipient serology, as follows:

- CMV seronegative (donor and recipient): No prophylaxis, no antigenemia (or PCR) checks
- CMV seropositive (donor or recipient):
  - No history of CMV infection: CMV surveillance testing (antigenemia or PCR) every 1-4 weeks
  - History of CMV infection or disease: Weekly CMV surveillance testing (antigenemia or PCR) and preemptive treatment as during the first 100 days

Some investigators have advocated early empirical treatment of influenza with neuraminidase inhibitors during influenza outbreaks by using prediction rules based on symptoms and signs [110,111], although there is no evidence to support this practice.

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MUSCULOSKELETAL

See Tables 12 and 13. Musculoskeletal complications after HCT are caused by chronic GVHD and its treatment with corticosteroids. The most frequent problems include fasciitis, sclerotic contractures and limitation in the range of motion, steroid-induced myopathy, and osteoporosis. The topic of fasciitis and sclerotic changes has been partly covered under Skin and Appendages.

This section will focus on rehabilitation for disorders of mobility associated with fasciitis, contractures, and steroid myopathy and on prevention and management of osteopenia/osteoporosis.

Rehabilitation in Patients with Chronic GVHD

Impairments such as joint contractures, limb swelling, and muscle atrophy and weakness are often seen in chronic GVHD. Functional loss associated with these impairments includes decreased mobility, fatigue, and a decreased ability to perform activities of daily living or work-related activities [112,113]. Assessment of the patient depends on comprehensive neuromusculoskeletal examination testing strength, range of motion of affected joints, limb girth, pain

Table 12. *Ancillary Therapy and Supportive Care Recommendations for Fasciitis, Contractures, and Steroid Myopathy*

Type of Intervention	Rating
Fasciitis/contractures	
Refer to physical therapy for quantitative range of motion measurements, to provide the patient with stretching exercises, and to monitor progress	AIII
Evaluation of range of motion at each clinic visit	AIII
Daily stretching exercises at home	AIII
Physical therapy stretching 2-3 times a week (severe impairment)	AIII
Surgical release	DIII
Steroid myopathy and deconditioning	
Strengthening: isometric, isotonic, isokinetic exercises	AII
Decreased stamina: aerobic exercise—should be progressive with increase in duration and resistance to increase heart rate	AIII

mobility, stamina and activities of daily living, and subjective measurements of disability. Whenever possible, treatment should be aimed at early intervention and prevention of severe joint contractures and deconditioning. Restoration of range of motion, strength, mobility, and relief of pain are some of the essential rehabilitation goals [114-116]. Options include aggressive physical therapy or a home-based program. These considerations emphasize the central role of physical and occupational therapies in the multidisciplinary team caring for patients with chronic GVHD.

Prevention and Management of Osteoporosis

Bone mineral metabolism is disturbed after allogeneic HCT, even at >6 years [117-120]. The abnormalities described after HCT include increased bone resorption and decreased bone formation, with consequent osteopenia and, less frequently, osteoporosis. After HCT, bone mineral density (BMD) of the femoral neck may be more affected than the vertebrae, unlike postmenopausal osteoporosis [121-123]. The recommendations for prevention and treatment of osteoporosis in patients with chronic GVHD are based on experience with osteoporosis in other diseases such as breast and prostate cancers and on expert consensus.

In patients with chronic GVHD, a baseline calcium (total and ionized) and vitamin D levels should be tested. These tests should be repeated at least annually when normal or as clinically indicated when abnormal or predicted to become abnormal. The consideration of secondary causes of osteoporosis at this stage is also critical. Referral to an endocrinologist is warranted whenever an endocrine, secondary cause of osteoporosis such as hyperparathyroidism is suspected [119].

BMD measurement by dual-energy x-ray absorptiometric scans is recommended in patients with chronic GVHD. The resulting T score indicates the number of SDs above or below the average BMD for healthy white women. T scores <-1.5 indicate osteopenia and those <-2.5 indicate osteoporosis. BMD studies should be repeated yearly for the first 3 years after HCT and, if BMD is stable, every 2-3 years thereafter [119].

Management consists of calcium and vitamin D supplementation and antiresorptive therapy.

Calcium and vitamin D. Replacement is justified in deficient states or when patients are postmenopausal or at high risk of developing deficiency [124,125] but is not adequate in patients with osteoporosis [126].

Antiresorptive therapy. In patients in whom steroid therapy is expected to last >3 months, a BMD study should be performed and antiresorptive therapy should be started regardless of the results. Preferred antiresorptive therapy includes hormonal replacement or bisphosphonates [126-128]. Secondary options include raloxifene or calcitonin [126].

In patients who are not taking steroids for extended periods, recommendations are based on BMD T scores. Antiresorptive therapy is indicated if the BMD T score is <-1.5. Patients with T scores >-1.5 should be followed closely with BMD studies yearly for 3 years and, if stable, every 2-3 years thereafter.

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PSYCHOSOCIAL

See Table 14. Studies of late effects in patients after allogeneic HCT have suggested that chronic GVHD produces deleterious consequences for multi-

Table 13. *Recommendations for Prevention and Management of Osteoporosis*

Recommendation	Rating
Calcium and vitamin D replacement in deficient states, postmenopausal women, and high risk of deficiency	AIb
Antiresorptive therapy when prolonged corticosteroid administration (>3 mo)	AIIb
Antiresorptive therapy	
In patients off steroids and T score ≤−1.5	AIIb
In patients with higher T scores	DIII
Pediatric considerations	
The definition of decreased bone mineral density in children uses age- and sex-normalized SD scores (Z scores) rather than T scores. Osteopenia is a Z score <1.5 and osteoporosis is a Z score <−2.5. The incorrect application of T scores to children may lead to inappropriate misdiagnosis and overtreatment	
The published use of bisphosphonates in children is limited, and most experience is with pamidronate	
Use of oral bisphosphonates is even less studied than the use of parenteral formulations	

Table 14. *Ancillary Therapy and Supportive Care Recommendations for Psychosocial Issues*

Type of Intervention	Rating
Neuropsychological testing and rehabilitation for long-term survivors (>1 y) when cognitive deficits impair work or disrupt daily activities and safety	**CIII**
Referral to a specialist and appropriate treatment of depression, anxiety, and pain	**BIII**
Supportive and cognitive behavioral interventions for body image issues, sexual functioning, and fatigue	**BIII**
Pediatric considerations	
No substantive differences	

dimensional functioning and quality of life [92,129-132]. The literature has shown that patients with chronic GVHD report significantly more fatigue, pain, bowel changes, and dyspareunia than do those without chronic GVHD [92,132]. Physical, sexual, and social functioning is also lower in patients with chronic GVHD [92,132], and patients with more severe chronic GVHD have impaired physical and psychosocial recovery at 1 year after HCT [131] and long term [130] (Table 14). Chiodi et al [129] reported that chronic GVHD was the most important factor influencing diminished vocation and domestic role function and that chronic GVHD negatively affected family interactions and social activities. Although extensive chronic GVHD was a consistent negative predictor of impaired quality of life, continued immunosuppressive therapy itself did not appear to have a negative influence on quality of life [129].

Research has suggested that the experience of long survivorship after allogeneic HCT and its associated symptoms and late term effects, including chronic GVHD, can cause negative changes in self-concept [133], mood disturbance [131,134,135] including depression [131,134,136] and anxiety [131,137], psychosocial distress [134,138], and diminished social relationships and social function [134,139,140].

Some of the more prevalent psychosocial situations associated with chronic GVHD include neurocognitive impairment and mood alterations, altered body image, sexual dysfunction, and fatigue.

Neurocognitive Functioning, Depression, and Anxiety

Neurocognitive performance usually decreases shortly after HCT and recovers in most patients by 1 year [131]. Chronic GVHD has not been associated with any specific intellectual function deficits, but immunosuppressive medications have not been specifically tested as risk factors in children. Thus, neuropsychological testing may be indicated if patients or families report difficulty with home- or work-related cognitive or motor tasks that persist for >1 year after HCT. Reassurance and rehabilitation approaches that teach adaptive strategies can be useful.

Depressive symptoms are more severe and longer term in HCT recipients who have extensive chronic GVHD [133]. Depression and other mental status changes should be assessed concurrently with neurocognitive function, because depression or distress is often the source of complaints about concentration or memory [133]. The presence of chronic GVHD does not alter the usual management of depression and anxiety.

Body Image

Body image can be greatly affected by the manifestations and treatment of chronic GVHD. Body image is dynamic and affects an individual's feelings of body function, appearance, and sensations [141]. Across the age spectrum, patients with chronic GVHD who have changes in their body image may experience frustration, anger, anxiety, guilt, and depression. In particular, school-age children and adolescents face the additional challenge of peer acceptance. Changes in body image significantly affect their ability to meet these psychosocial and developmental needs. In adults, role abandonment and ineffectiveness, social isolation and loneliness, and sexual dysfunction are also potential sequelae. Provision of psychological and emotional support to patients and their caregivers, education, cognitive-behavioral interventions, and medications may be helpful if depression or anxiety is also present.

Sexual Dysfunction

Sexual problems for men and women may include fatigue, loss of partnership role and independence, infertility, gonadal ablation, sleep dysfunction, financial concerns, and changes in body image involving hair loss, rash, sclerosis, body weight, body odors, and bowel and bladder function. Interruption of sexual activity and sexual difficulties for prolonged periods after HCT are common manifestations [142]. Therapeutic options for sexual dysfunction usually begin with counseling: identifying the problems with the couple or individual, helping overcome anxiety, and addressing the concerns of patients who do not have a partner. Specific therapies may include gradual resumption of sexual activities, positions, use of pillows and props, creating an intimate atmosphere, and setting a time of day when the patient is least tired. Couples, regardless of sexual orientation, need to know that pleasure from touching, that does not necessarily culminate in intercourse, almost always remains.

Fatigue

Fatigue is defined as a persistent and subjective sense of tiredness that interferes with usual functioning [143]. The biochemical, physiological, psychological, and behavioral mechanisms of this syndrome are poorly understood [144]. Although little is known about the prevalence, correlates, or predictors of fatigue in individuals with chronic GVHD, empirical evidence and clinical practice support a conclusion that fatigue remains a prevalent and distressing symptom for many years after allogeneic HCT [130,145,146].

Energy conservation measures (set priorities, delegate, pace, schedule activities at time of peak energy, structure daily routine), initiation of a low impact or seated exercise program, referral to physical therapy and rehabilitation for exercise prescription, psychosocial interventions (stress management, relaxation, cognitive behavioral therapy, or support group), nutrition consultation, management of other concurrent distressing symptoms including pain, avoidance or limitation of pharmacologic agents with sedating side effects, efforts to improve sleep patterns (sleep hygiene, hypnotics), attention-restoring therapy (eg, natural environment activities), distraction (eg, music, socializing), and psychostimulants (eg, methylphenidate, antidepressants) may be helpful. The National Comprehensive Cancer Network has produced a consensus document summarizing the available interventions for management of fatigue during and after cancer treatment [143].

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NIH CONSENSUS DEVELOPMENT PROJECT ON CRITERIA FOR CLINICAL TRIALS IN CHRONIC GVHD STEERING COMMITTEE

Steven Pavletic and Georgia Vogelsang (project chairs), LeeAnn Jensen (planning committee chair), Lisa Filipovich (diagnosis and staging), Howard Shulman (histopathology), Kirk Schultz (biomarkers), Dan Couriel (ancillary and supportive care), Stephanie Lee (design of clinical trials), and James Ferrara, Mary Flowers, Jean Henslee-Downey, Paul Martin, Barbara Mittleman, Shiv Prasad, Donna Przepiorka, Douglas Rizzo, Daniel Weisdorf, and Roy Wu (members). The project group also recognizes contributions of numerous colleagues in the field of blood and marrow transplantation, medical specialists and consultants, pharmaceutical industry, and the NIH and US Food and Drug Administration professional staff for intellectual input, dedication, and enthusiasm on the road toward completion of these documents.

Appendix A. *Evidence-Based Rating System for Ancillary Therapy and Supportive Care Guidelines in Chronic Graft-versus-Host Disease*

Category	Definition
Strength of the recommendation	
A	Should always be offered.
B	Should generally be offered.
C	Evidence for efficacy is insufficient to support a recommendation for or against, or evidence for efficacy might not outweight adverse consequences, or cost of the approach. Optional.
D	Moderate evidence for lack of efficacy or for adverse outcome supports a recommendation against use. Should generally not be offered.
E	Good evidence for lack of efficacy or for adverse outcome supports a recommendation against use. Should never be offered.
Quality of evidence supporting the recommendation	
I	Evidence from ≥1 properly randomized, controlled trial.
II	Evidence for ≥1 well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferable from >1 center), or from multiple time series or dramatic results from uncontrolled experiments.
III	Evidence from opinions of respected authorities based on clinical experience, descriptive.
Qualifier for categories I and II	
a	Evidence derived directly from study(s) in graft-versus-host disease.
b	Evidence derived indirectly from study(s) in analogous or other pertinent disease.

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